DIVIGEL - estradiol gel
Upsher-Smith Laboratories, Inc.

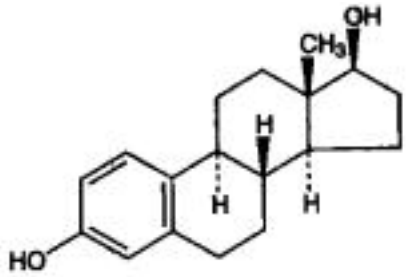
Rx only

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER
Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses. (See WARNINGS, Malignant neoplasms, Endometrial cancer.)

CARDIOVASCULAR AND OTHER RISKS
Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia. (See CLINICAL STUDIES and WARNINGS, Cardiovascular disorders and Dementia.)
The estrogen-alone substudy of the Women's Health Initiative (WHI) reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 6.8 years and 7.1 years, respectively, of treatment with oral conjugated estrogens (CE 0.625 mg) alone per day, relative to placebo. (See CLINICAL STUDIES and WARNINGS, Cardiovascular disorders.)
The estrogen-plus-progestin substudy of the WHI reported increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) per day, relative to placebo. (See CLINICAL STUDIES and WARNINGS, Cardiovascular disorders and Malignant neoplasms, *Breast cancer*.)
The Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with CE 0.625 mg alone and during 4 years of treatment with CE 0.625 mg combined with MPA 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See CLINICAL STUDIES, WARNINGS, Dementia, and PRECAUTIONS, Geriatric Use.)
Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

Divigel® (estradiol gel) 0.1% is a clear, colorless gel, which is odorless when dry. It is designed to deliver sustained circulating concentrations of estradiol when applied once daily to the skin. The gel is applied to a small area (200 cm^2) of the thigh in a thin, quick-drying layer. Divigel® is available in three doses of 0.25, 0.5, and 1.0 g for topical application (corresponding to 0.25, 0.5, and 1.0 mg estradiol, respectively).
The active component of the topical gel is estradiol.
Estradiol is a white crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17β-diol. It has an empirical formula of $C_{18}H_{24}O_2$ and molecular weight of 272.39. The structural formula is:



The remaining components of the gel (carbomer, ethanol, propylene glycol, purified water, and triethanolamine) are pharmacologically inactive.

CLINICAL PHARMACOLOGY

Divigel® provides estrogen therapy by delivering estradiol, the major estrogenic hormone secreted by the human ovary, to the systemic circulation following topical application.

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.
Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.
Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

Pharmacokinetics

A. Absorption
Estradiol diffuses across intact skin and into the systemic circulation by a passive absorption process, with diffusion across the stratum corneum being the rate-limiting factor.

In a 14-day, Phase 1, multiple-dose study, Divigel® demonstrated linear and approximately dose-proportional estradiol pharmacokinetics at steady state for both AUC_{0-24} and C_{max} following once daily dosing to the skin of either the right or left upper thigh (Table 1).

Table 1: Mean (%CV) Pharmacokinetic Parameters for Estradiol (uncorrected for baseline) on Day 14 Following Multiple Daily Doses of Divigel® 0.1%

Parameter (units)	**Divigel® 0.25 g**	**Divigel® 0.5 g**	**Divigel® 1.0 g**
AUC_{0-24} (pg•h/mL)	236 (94)	504 (149)	732 (81)
C_{max} (pg/mL)	14.7 (84)	28.4 (139)	51.5 (86)
C_{avg} (pg/mL)	9.8 (92)	21 (148)	30.5 (81)
t_{max}* (h)	16 (0, 72)	10 (0, 72)	8 (0, 48)
E2:E1 ratio	0.42	0.65	0.65

*Median (Min, Max).

Steady-state serum concentration of estradiol are achieved by day 12 following daily application of Divigel® to the skin of the upper thigh. The mean (SD) serum estradiol levels following once daily dosing at day 14 are shown in Figure 1.

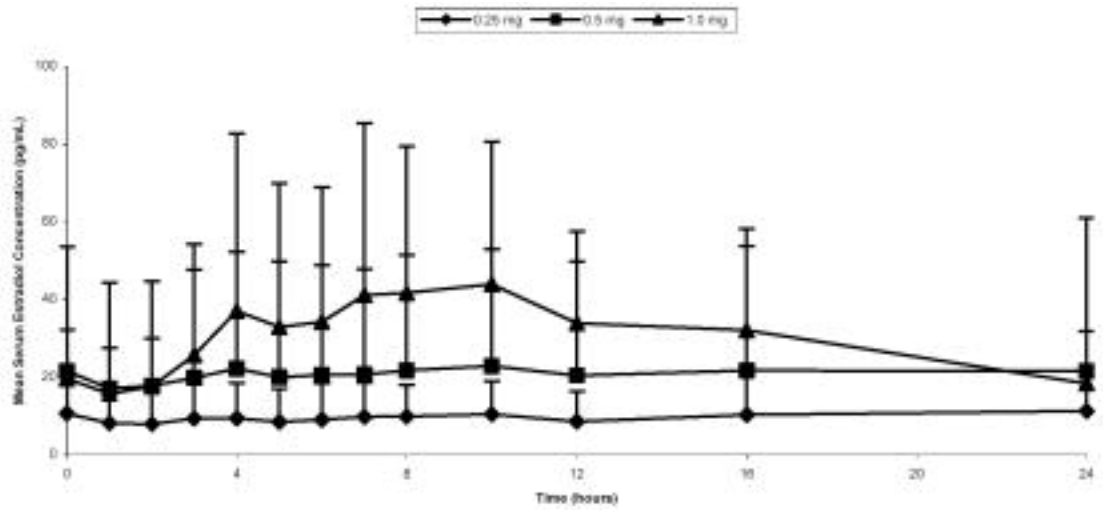


Figure 1: Mean (SD) Serum Estradiol Concentrations (Values Uncorrected for Baseline) on Day 14 Following Multiple Daily Doses of Divigel 0.1%

The effect of sunscreens and other topical lotions on the systemic exposure of Divigel® has not been evaluated. Studies conducted using topical estrogen gel approved products have shown that sunscreens have the potential for changing the systemic exposure of topically applied estrogen gels.

B. Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

C. Metabolism

Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Estradiol from Divigel® avoids first pass metabolism and provides estradiol/estrone ratios at steady state in the range of 0.42 to 0.65.

D. Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. The apparent terminal half-life for estradiol was about 10 hours following administration of Divigel®.

E. Special Populations

Divigel® has been studied only in postmenopausal women. No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

F. Drug Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice, may increase plasma concentrations of estrogens and result in side effects.

G. Potential for Estradiol Transfer and Effects of Washing

As with most topical products, there is a potential for estradiol transfer following physical contact with Divigel® application sites. The effect of estradiol transfer was evaluated in healthy postmenopausal women who topically applied 1.0 g of Divigel® (single dose) on one thigh. One and 8 hours after gel application, they engaged in direct thigh- to- arm contact with a partner for 15 minutes. While some elevation of estradiol levels over baseline was seen in the male subjects, the degree of transferability in this study was inconclusive.

The effect of application site washing on skin surface levels and serum concentrations of estradiol was determined in 16 healthy postmenopausal women after application of 1.0 g of Divigel® to a 200 cm^2 area on the thigh. Washing the application site with soap and water 1 hour after application removed all detectable amounts of estradiol from the surface of the skin, and resulted in a 30-38% decrease in the mean total 24-hour exposure to estradiol.

Clinical Studies

Effects on Vasomotor Symptoms

A randomized, double-blind, placebo-controlled trial evaluated the efficacy of 12-week treatment with three different daily doses of Divigel® for vasomotor symptoms in 495 postmenopausal women (86.5% White; 10.1% Black) between 34 and 89 years of age (mean age 54.6) who had at least 50 moderate to severe hot flushes per week at baseline (2 week period prior to treatment). Subjects applied placebo, Divigel® 0.25 g (0.25 mg estradiol), Divigel® 0.5 g (0.5 mg estradiol) or Divigel® 1.0 g (1.0 mg estradiol) once daily to the thigh. Reductions in both the median daily frequency and the median daily severity of moderate to severe hot flushes were statistically significant for the 0.5 g/day and the 1.0 g/day Divigel® doses when compared to placebo at week 4. Statistically significant reductions in both the median daily frequency and the median daily severity of moderate to severe hot flushes for the Divigel® 0.25 g/day dose when compared to placebo were delayed to week 7. There were statistically significant reductions in median

daily frequency and severity of hot flushes for all three Divigel® doses (0.25 g/day, 0.5 g/day and 1.0 g/day) compared to placebo at week 12. See Table 2 for results.

Table 2: Summary of Change From Baseline in the Median Daily Frequency and Severity of Hot Flushes during Divigel® Treatment (ITT Population)

	Divigel®			**Placebo**
Evaluation	0.25 g/day N=121	0.5 g/day N=119	1.0 g/day N=124	N=124
Frequency of Daily Hot Flushes				
Baseline Median	9.72	9.24	9.64	9.32
Median Change: Week 4	-5.00	-5.73	-7.20	-3.63
p-value†	0.132	0.011	<0.001	
Median Change: Week 7	-6.62	-7.14	-7.71	-4.37
p-value†	<0.001	<0.001	<0.001	
Median Change: Week 12	-6.88	-7.29	-8.35	-4.48
p-value†	<0.001	<0.001	<0.001	
Severity of Daily Hot Flushes				
Baseline Median	2.52	2.51	2.52	2.54
Median Change: Week 4	-0.07	-0.18	-0.47	-0.04
p-value†	0.283	<0.001	<0.001	
Median Change: Week 7	-0.24	-0.46	-1.06	-0.06
p-value†	<0.001	<0.001	<0.001	
Median Change: Week 12	-0.33	-0.56	-1.69	-0.13
p-value†	0.021	0.002	<0.001	

†p-values from the van Elteren's test stratified by pooled center; comparison in median change was significant if $p<0.05$

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of either the use of oral conjugated estrogens (CE 0.625 mg) alone per day or in combination with medroxyprogesterone acetate (CE 0.625 mg/MPA 2.5 mg) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction (MI), silent MI and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer (only in the estrogen-plus-progestin substudy), colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The estrogen-alone substudy was stopped early because an increased risk of stroke was observed and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen alone in predetermined primary endpoints. Results of the estrogen-alone substudy, which included 10,739 women (average age of 63 years, range 50 to 79; 75.3% White, 15.1% Black, 6.1% Hispanic, 3.6% Other), after an average follow-up of 6.8 years are presented in Table 3.

Table 3: Relative And Absolute Risk Seen In The Estrogen-Alone Substudy Of WHI[a]

Event	**Relative Risk CE vs. Placebo**	**Placebo n = 5,429**	**CE n = 5,310**
	(95% nCI[a])	**Absolute Risk per 10,000 Women-Years**	
CHD events[b]	0.95 (0.79- 1.16)	56	53
Nonfatal MI[b]	*0.91 (0.73-1.14)*	*43*	*40*
CHD death[b]	*1.01 (0.71- 1.43)*	*16*	*16*
Stroke[c]	1.39 (1.10-1.77)	32	44
Deep vein thrombosis[b,d]	1.47 (1.06-2.06)	15	23

Pulmonary embolism[b]	1.37 (0.90-2.07)	10	14
Invasive breast cancer[b]	0.80 (0.62-1.04)	34	28
Colorectal cancer[c]	1.08 (0.75-1.55)	16	17
Hip fracture[c]	0.61 (0.41-0.91)	17	11
Vertebral fractures[c,d]	0.62 (0.42-0.93)	17	11
Total fractures[c,d]	0.70 (0.63-0.79)	195	139
Death due to other causes[c,e]	1.08 (0.88-1.32)	50	53
Overall mortality[c,d]	1.04 (0.88-1.32)	78	81
Global index[c,f]	1.01 (0.91-1.12)	190	192

[a] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons

[b] Results are based on centrally adjudicated data for an average follow-up of 7.1 years

[c] Results are based on an average follow-up of 6.8 years

[d] Not included in Global Index

[e] All deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease

[f] A subset of the events was combined in a “global index”, defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes

For those outcomes included in the WHI “global index” that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was 6 fewer hip fractures. The absolute excess risk of events included in the “global index” was a nonsignificant 2 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

Final centrally adjudicated results for CHD events and centrally adjudicated results for invasive breast cancer incidence from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE alone compared with placebo (see Table 3).

The estrogen-plus-progestin substudy was also stopped early because, according to the predefined stopping rule, after an average follow-up of 5.2 years of treatment, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index.” The absolute excess risk of events included in the “global index” was 19 per 10,000 women-years (RR 1.15, 95% nCI 1.03-1.28).

For those outcomes included in the WHI “global index” that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women years in the group treated with CE/MPA were 6 more CHD events, 7 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 7 fewer colorectal cancers and 5 fewer hip fractures. (See **BOXED WARNINGS, WARNINGS**, and **PRECAUTIONS**.)

Results of the estrogen-plus-progestin substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.8% Black, 5.4% Hispanic, 3.9% Other), are presented in Table 4 below. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 4: Relative And Absolute Risk Seen in the Estrogen-Plus Progestin Substudy of WHI at an Average of 5.6 Years[a]

Event[c]	Relative Risk CE/MPA vs. Placebo (95% nCI[b])	Placebo n = 8102	CE/MPA n = 8506
		Absolute Risk per 10,000 women-years	
CHD events	1.24 (1.00-1.54)	33	39
Non-fatal MI	*1.28 (1.00-1.63)*	*25*	*31*
CHD death	*1.10 (0.70-1.75)*	*8*	*8*
All strokes	1.31 (1.02-1.68)	24	31
Ischemic stroke	*1.44 (1.09 -1.90)*	*18*	*26*
Deep vein thrombosis	1.95 (1.43 – 2.67)	13	26
Pulmonary embolism	2.13 (1.45-3.11)	8	18
Invasive breast cancer[c]	1.24 (1.01-1.54)	33	41

Invasive colorectal cancer	0.56 (0.38-0.81)	16	9
Endometrial cancer	0.81 (0.48-1.36)	7	6
Cervical cancer	1.44 (0.47-4.42)	1	2
Hip fracture	0.67 (0.47-0.96)	16	11
Vertebral fractures	0.65 (0.46-0.92)	17	11
Lower arm/wrist fractures	0.71 (0.59-0.85)	62	44
Total fractures	0.76 (0.69-0.83)	199	152

[a] Results are based on centrally adjudicated data. Mortality data was not part of the adjudicated data; however, data at 5.2 years of follow-up showed no difference between the groups in terms of all-cause mortality (RR 0.98, 95% nCI 0.82-1.18)

[b] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

[c] Includes metastatic and non-metastatic breast cancer, with the exception of in situ breast cancer

Women's Health Initiative Memory Study

The estrogen-alone Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI, enrolled 2,947 predominantly healthy postmenopausal women 65 years of age and older (45% were aged 65 to 69 years, 36% were 70 to 74 years, and 19% were 75 years of age and older) to evaluate the effects of conjugated estrogens (CE 0.625 mg) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group (37 per 10,000 women-years) and 19 in the placebo group (25 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the estrogen-alone group was 1.49 (95% confidence interval (CI), 0.83-2.66) compared to placebo. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS, WARNINGS, Dementia,** and **PRECAUTIONS, Geriatric Use.)**

The estrogen-plus-progestin WHIMS substudy enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were aged 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) daily on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the estrogen-plus-progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21-3.48) compared to placebo.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60). It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNING**, **WARNINGS, Dementia**, and **PRECAUTIONS, Geriatric Use**.)

INDICATIONS AND USAGE

Divigel® (estradiol gel) 0.1% is indicated in the treatment of moderate to severe vasomotor symptoms associated with menopause.

CONTRAINDICATIONS

Estrogen products, including Divigel® (estradiol gel) 0.1%, should not be used in women with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of cancer of the breast.
3. Known or suspected estrogen-dependent neoplasia.
4. Active deep vein thrombosis, pulmonary embolism, or history of these conditions.
5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6. Liver dysfunction or disease.
7. Known hypersensitivity to the ingredients of Divigel®.
8. Known or suspected pregnancy. There is no indication for Divigel® in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See **PRECAUTIONS**.)

WARNINGS

See **BOXED WARNINGS**.

1. Cardiovascular Disorders

Estrogen-alone therapy has been associated with an increased risk of stroke and deep vein thrombosis (DVT).
Estrogen-plus progestin therapy has been associated with an increased risk of myocardial infarction as well as stroke, venous thrombosis and pulmonary embolism.
Should any of these occur or be suspected, estrogens should be discontinued immediately.
Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

a. Stroke

In the estrogen-alone substudy of the Women's Health Initiative (WHI), a statistically significant increased risk of stroke was observed in women receiving CE 0.625 mg daily compared to placebo (44 versus 32 per 10,000 women-years). The increase in risk was observed in year 1 and persisted. (See **CLINICAL STUDIES**.)

In the estrogen-plus-progestin substudy of the WHI study, a statistically significant increased risk of stroke was reported in women receiving CE/MPA 0.625 mg/2.5 mg daily compared to women receiving placebo (31 versus 24 per 10,000 women-years). The increase in risk was demonstrated after the first year and persisted.

b. Coronary heart disease

In the estrogen-alone substudy of WHI, no overall effect on coronary heart disease (CHD) events (defined as non-fatal MI, silent MI, or death, due to CHD) was reported in women receiving estrogen-alone compared to placebo. (See **CLINICAL STUDIES**.)

In the estrogen-plus-progestin substudy of WHI, no statistically significant increase of CHD events was reported in women receiving CE/MPA compared to women receiving placebo (39 vs. 33 per 10,000 women-years). An increase in relative risk was demonstrated in year one and a trend toward decreasing relative risk was reported in years 2 through 5.

In postmenopausal women with documented heart disease (n=2,763, average age 66.7 years), a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study (HERS)) treatment with CE/MPA (0.625 mg/2.5 mg per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Participation in an open label extension of the original HERS trial (HERS II) was agreed to by 2,321 women. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of non-fatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

c. Venous Thromboembolism

In the estrogen-alone substudy of WHI the risk of VTE (DVT and pulmonary embolism [PE]), was reported to be increased for women taking conjugated estrogens compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 vs. 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first two years. (See **CLINICAL STUDIES**.)

In the estrogen-plus-progestin substudy of WHI, a statistically significant two-fold greater rate of VTE, was reported in women receiving CE/MPA compared to women receiving placebo (35 vs. 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 vs. 13 per 10,000 women-years) and PE (18 vs. 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted. (See **CLINICAL STUDIES**.)

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant Neoplasms

a. Endometrial cancer

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risk of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. Breast Cancer

In some studies, the use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) (see **CLINICAL STUDIES**). The results from observational studies are generally consistent with those of the WHI clinical trial.

Observational studies have also reported an increased risk of breast cancer for estrogen-plus-progestin combination therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. For both findings, the excess risk increased with duration of use, and appeared to return to baseline over about five years after stopping treatment (only the observational studies have substantial data on risk after stopping). In these studies, the risk of breast cancer was greater, and became apparent earlier, with estrogen-plus-progestin combination therapy as compared to estrogen-alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogens or among different estrogen-plus-progestin combinations, doses, or routes of administration.

In the estrogen-alone substudy of WHI, after an average of 7.1 years of follow-up, CE (0.625 mg daily) was not associated with an increased risk of invasive breast cancer (RR 0.80, 95 % nCI 0.62-1.04).

In the estrogen-plus-progestin substudy, after a mean follow-up of 5.6 years, the WHI substudy reported an increased risk of breast cancer. In this substudy, prior use of estrogen-alone or estrogen/progestin combination hormone therapy was reported by 26% of the women. The relative risk of invasive breast cancer was 1.24 (95% nCI, 1.01-1.54), and the absolute risk was 41 versus 33 cases per 10,000 women-years, for estrogen-plus-progestin compared with placebo, respectively. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for estrogen-plus-progestin compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for estrogen-plus-progestin compared with placebo. In the WHI trial, invasive breast cancers were larger and diagnosed at a more advanced stage in the estrogen-plus-progestin group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen-alone and estrogen-plus-progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

3. Dementia

In the estrogen-alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomized women aged 65 to 79 years was randomized to CE (0.625 mg daily) or placebo. In the estrogen-plus-progestin WHIMS, a population of 4,532 postmenopausal women aged 65 to 79 years was randomized to CE/MPA (0.625 mg/2.5 mg daily) or placebo.

In the estrogen-alone substudy, after an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE alone versus placebo was 1.49 (95% CI, 0.83-2.66). The absolute risk of probable dementia for CE alone versus placebo was 37 versus 25 cases per 10,000 women-years.

In the estrogen-plus-progestin substudy, after an average follow-up of 4 years, 40 women in the estrogen-plus-progestin group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen-plus-progestin versus placebo was 2.05 (95% CI, 1.21-3.48). The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60). Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (see **BOXED WARNINGS** and **PRECAUTIONS,** and **Geriatric Use**.)

4. Gallbladder Disease

A two- to four-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

5. Hypercalcemia
Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

6. Visual Abnormalities
Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

PRECAUTIONS

A. General

1. Addition of a progestin when a woman has not had a hysterectomy
Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer, adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL), and impairment of glucose tolerance.

2. Elevated blood pressure
In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

3. Hypertriglyceridemia
In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

4. Impaired liver function and past history of cholestatic jaundice
Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

5. Hypothyroidism
Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored to maintain their free thyroid hormone levels in an acceptable range.

6. Fluid retention
Estrogens may cause some degree of fluid retention. Because of this, patients who have conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

7. Hypocalcemia
Estrogens should be used with caution in individuals with severe hypocalcemia.

8. Ovarian cancer
The estrogen-plus-progestin substudy of the WHI reported that after an average follow-up of 5.6 years, the relative risk for ovarian cancer for estrogen-plus-progestin versus placebo was 1.58 (95% nCI, 0.77-3.24), but was not statistically significant. The absolute risk for estrogen-plus-progestin versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen only products in particular for 10 or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

9. Exacerbation of endometriosis
Endometriosis may be exacerbated with administration of estrogens. Malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

10. Exacerbation of other conditions

Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

11. Photosensitivity/Photoallergy

The effects of direct sun exposure to Divigel® application sites have not been evaluated in clinical trials. Nonclinical studies in guinea pigs showed no phototoxicity or photosensitivity. In addition, Divigel® has been shown to absorb light primarily at wavelengths below 290 nm. Therefore, Divigel® is not considered to have photosensitizing potential.

12. Sunscreen application

Studies conducted using other approved topical estrogen gel products have shown that sunscreens have the potential for changing the systemic exposure of topically applied estrogen gels. The effect of concomitant application of sunscreen and Divigel® to the same application site has not been clinically evaluated.

13. Miscellaneous

Alcohol based gels are flammable. Avoid fire, flame, or smoking until the gel has dried.

Occlusion of the area where the topical drug product is applied with clothing or other barriers is not recommended until the gel is completely dried.

14. Potential for Estradiol Transfer and Effects of Washing

There is a potential for drug transfer from one individual to the other following physical contact of Divigel® application sites. In a study to evaluate transferability to males from their female contacts, there was some elevation of estradiol levels over baseline in the male subjects, however, the degree of transferability in this study was inconclusive. Patients are advised to avoid skin contact with other subjects until the gel is completely dried. The site of application should be covered (clothed) after drying.

Washing the application site with soap and water 1 hour after application resulted in a 30 to 38% decrease in the mean total 24-hour exposure to estradiol. Therefore, patients should refrain from washing the application site for at least one hour after application.

B. Information for Patients

Physicians and pharmacists are advised to discuss the **PATIENT INFORMATION** leaflet with patients for whom they prescribe or dispense Divigel®.

C. Laboratory Tests

Estrogen administration should be initiated at the lowest dose approved for the treatment of moderate-to-severe vasomotor symptoms associated with menopause and then guided by clinical response rather than by serum hormone levels (e.g., estradiol, FSH).

D. Drug and Laboratory Test Interactions

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.

3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), sex hormone binding globulin (SHBG) leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-l-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility

See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS**.

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis and liver.

F. Pregnancy

Estrogen products, including Divigel®, should not be used in pregnancy. (See **CONTRAINDICATIONS**.)

G. Nursing Mothers

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving estrogen therapy. Caution should be exercised when estrogen products, including Divigel®, are administered to a nursing woman.

H. Pediatric Use

Safety and efficacy of Divigel® in pediatric patients has not been established.

I. Geriatric Use

There have not been sufficient numbers of geriatric patients involved in studies utilizing Divigel® to determine whether those over 65 years of age differ from younger subjects in their response to Divigel®.

Of the total number of subjects in the estrogen-alone substudy of the Women's Health Initiative (WHI), 46% (n=4,943) were 65 years and older, while 7.1% (n=767) were 75 years and older. There was a higher relative risk (CE versus placebo) of stroke in women less than 75 years of age compared to women 75 years and older.

In the estrogen-alone substudy of the Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomized women, aged 65 to 79 years, was randomized to CE (0.625 mg per day) or placebo. After an average follow-up of 5.2 years, the relative risk (CE versus placebo) of probable dementia was 1.49 (95% CI, 0.83-2.66). The absolute risk of developing probable dementia with estrogen alone was 37 vs. 25 cases per 10,000 women-years with placebo.

Of the total number of subjects in the estrogen-plus-progestin substudy of the WHI, 44% (n=7,320) were 65 years and older, while 6.6% (n=1,095) were 75 years and older. There was a higher relative risk (CE/MPA versus placebo) of stroke and invasive breast cancer in women 75 and older compared to women less than 75 years of age. In women greater than 75, the increased risk of non-fatal stroke and invasive breast cancer observed in the estrogen-plus-progestin combination group compared to the placebo group was 75 vs. 24 per 10,000 women-years and 52 vs. 12 per 10,000 women years, respectively.

In the estrogen-plus-progestin substudy of WHIMS, a population of 4,532 postmenopausal women, aged 65 to 79 years, was randomized to CE/MPA (CE 0.625 mg/2.5 mg daily) or placebo. In the estrogen-plus-progestin group, after an average follow-up of 4 years, the relative risk (CE/MPA versus placebo) of probable dementia was 2.05 (95% CI, 1.21-3.48). The absolute risk of developing probable dementia with CE/MPA was 45 vs. 22 cases per 10,000 women-years with placebo.

Seventy-nine percent of the cases of probable dementia occurred in women that were older than 70 for the CE group, and 82 percent of the cases of probable dementia occurred in women who were older than 70 in the CE/MPA group. The most common classification of probable dementia in both the treatment groups and placebo groups was Alzheimer's disease.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall risk of probable dementia was 1.76 (95% CI, 1.19-2.60). Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS,** and **WARNINGS, Dementia**.)

ADVERSE REACTIONS

See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS**.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Divigel® was studied at doses of 0.25, 0.5 and 1.0 g/day in a 12-week, double-blind, placebo-controlled study that included a total of 495 postmenopausal women (86.5% Caucasian). The adverse events that occurred at a rate greater than 5% in any of the treatment groups are summarized in Table 5.

Table 5: Number (%) of Subjects with Common Adverse Events* in a 12-Week Placebo- Controlled Study of Divigel®

	Divigel®			**Placebo**
SYSTEM ORGAN CLASS **Preferred Term**	**0.25 g/day** **N=122** **n (%)**	**0.5 g/day** **N=123** **n (%)**	**1.0 g/day** **N=125** **n (%)**	**N=125** **n (%)**
INFECTIONS & INFESTATIONS				

Nasopharyngitis	7 (5.7)	5 (4.1)	6 (4.8)	5 (4.0)
Upper Respiratory Tract Infection	7 (5.7)	3 (2.4)	2 (1.6)	2 (1.6)
Vaginal mycosis	1 (0.8)	3 (2.4)	8 (6.4)	4(3.2)
REPRODUCTIVE SYSTEM & BREAST DISORDERS				
Breast Tenderness	3 (2.5)	7 (5.7)	11 (8.8)	2 (1.6)
Metrorrhagia	5 (4.1)	7 (5.7)	12 (9.6)	2 (1.6)

* Adverse events reported by ≥5% of patients in any treatment group.

In a 12-week placebo-controlled study of Divigel®, application site reactions were seen in <1% of subjects.
The following additional adverse reactions have been reported with estrogen and/or progestin therapy.

1. **Genitourinary system:** Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea; increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer; vaginal discharge.

2. **Breasts:** Tenderness; enlargement, pain, nipple discharge, galactorrhea, fibrocystic breast changes; breast cancer; nipple pain.

3. **Cardiovascular:** Deep and superficial venous thrombosis, pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

4. **Gastrointestinal:** Nausea; vomiting; abdominal cramps; bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis; enlargement of hepatic hemangiomas; abdominal pain.

5. **Skin:** Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus; rash.

6. **Eyes:** Retinal vascular thrombosis, intolerance to contact lenses.

7. **Central Nervous System:** Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy; dementia.

8. **Miscellaneous:** Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthralgias; leg cramps; changes in libido; urticaria; angioedema; anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides; muscle cramps.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing drug products by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

When estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as clinically appropriate (e.g., 3-month to 6-month intervals) to determine if treatment is still necessary (see **BOXED WARNINGS** and **WARNINGS**). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Divigel® (estradiol gel) 0.1%, at doses of 0.25, 0.5, and 1.0 g/day, is indicated for topical use in the treatment of moderate to severe vasomotor symptoms associated with menopause. Each gram of Divigel® contains 1 mg of estradiol.

Patients should be treated with the lowest effective dose of Divigel®. Generally, women should be started at 0.25 gram Divigel® daily. Subsequent dosage adjustments may be made based upon the individual patient response. This dose should be periodically reassessed by the healthcare provider.

Divigel® should be applied once daily on the skin of either the right or left upper thigh. The application surface area should be about 5 by 7 inches (approximately the size of two palm prints). The entire contents of a unit dose packet should be applied each day. To avoid potential skin irritation, Divigel® should be applied to the right or left upper thigh on alternating days. Divigel® should not be applied on the face, breasts, or irritated skin or in or around the vagina. After application, the gel should be allowed to dry before dressing.

The application site should not be washed within 1 hour after applying Divigel®. Contact of the gel with eyes should be avoided. Hands should be washed after application.

HOW SUPPLIED

Divigel® (estradiol gel) 0.1% is a clear, colorless, smooth, opalescent gel supplied in single-dose foil packets of 0.25, 0.5, and 1.0 g, corresponding to 0.25, 0.5, and 1.0 mg estradiol, respectively.
NDC 0245-0880-30, carton of 30 packets, 0.25 mg estradiol per single-dose foil packet
NDC 0245-0881-30, carton of 30 packets, 0.5 mg estradiol per single-dose foil packet
NDC 0245-0882-30, carton of 30 packets, 1.0 mg estradiol per single-dose foil packet
Keep out of the reach of children.
Store at 20 to 25°C (68 to 77°F). Excursions permitted to 15 to 30°C (59 to 86°F). [See USP Controlled Room Temperature.]
Manufactured by
Orion Corporation Orion Pharma
Tengströminkatu 8
FI-20360 Turku
Finland
Distributed by
Upsher-Smith Laboratories, Inc.
Minneapolis, MN 55447
1-800-654-2299
Product of Finland
Revised June 2007

PATIENT INFORMATION
(Updated June 2007)

Divigel®
(estradiol gel) 0.1%

Read this PATIENT INFORMATION leaflet before you start using Divigel® and read what you get each time you refill your Divigel® prescription. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT Divigel® (AN ESTROGEN HORMONE)?

- Estrogens increase the chance of getting cancer of the uterus. Report any unusual vaginal bleeding right away while you are taking estrogens. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- Do not use estrogens, with or without progestins, to prevent heart disease, heart attacks, or strokes. Using estrogens, with or without progestins, may increase your chance of getting heart attacks, strokes, breast cancer, and blood clots.
- Do not use estrogens, with or without progestins, to prevent dementia. Using estrogens, with or without progestins, may increase your risk of dementia.

  You and your healthcare provider should talk regularly about whether you still need treatment with Divigel®.

What is Divigel®?

Divigel® is a medicine that contains an estrogen hormone (estradiol). Divigel® is a clear, colorless, smooth gel that is odorless when dry.

What is Divigel® used for?

Divigel® is used after menopause to:
- **Reduce moderate to severe hot flashes**

Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 to 55 years old. This drop in body estrogen levels causes the “change of life” or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes “surgical menopause.”
When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating (“hot flashes” or “hot flushes”). In some women, the symptoms are

mild, and they will not need estrogens. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether you still need treatment with Divigel®.

Who should not use Divigel®?

Do not start using Divigel® if you:

- **Have unusual vaginal bleeding**
- **Currently have or have had certain cancers**

Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should use Divigel®.

- **Had a stroke or heart attack in the past year**
- **Currently have or have had blood clots**
- **Currently have or have had liver problems**
- **Are allergic to Divigel® or any of its ingredients**

See the next section of this leaflet for a list of ingredients in Divigel®.

- **Think you may be pregnant**

TELL YOUR HEALTHCARE PROVIDER:

- **If you are breastfeeding**

The hormone in Divigel® can pass into your milk.

- **About all of your medical problems**

Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing); epilepsy (seizures); migraine; endometriosis; lupus; problems with your heart, liver, thyroid, or kidneys; or have high calcium levels in your blood.

- **About all the medicines you take**

This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Divigel® works. Divigel® may also affect how your other medicines work.

- **If you are going to have surgery or will be on bedrest**

You may need to stop using Divigel®.

What are the ingredients in Divigel®?

The active ingredient in Divigel® is estradiol.
The inactive ingredients are carbomer, ethanol, propylene glycol, purified water, and triethanolamine.

How should I use Divigel®?

1. Divigel® should be used once daily.
2. Start at the lowest dose and talk to your healthcare provider about how well that dose is working for you.
3. Divigel® should be used at the lowest dose possible for your treatment and only as long as needed.

You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with Divigel®.

Important things to remember when using Divigel®

- **Wash your hands with soap and water after applying the gel to reduce the chance that the medicine will be spread from your hands to other people.**
- Allow the gel to dry before dressing. Try to keep the area dry for as long as possible.
- Do not allow others to come in contact with the area of skin where you applied the gel for at least one hour after you apply Divigel®.

- You should not allow others to apply the gel for you. However, if this is necessary, the individual should wear a disposable plastic glove to avoid direct contact with Divigel®
- Do not apply Divigel® to your face, breast, or irritated skin.
- Never apply Divigel® in or around the vagina.
- **Divigel® contains alcohol. Alcohol based gels are flammable. Avoid fire, flame or smoking until the gel has dried.**

What should I do if I miss a dose?

If you miss a dose, do not double the dose on the next day to catch up. If your next dose is less than 12 hours away, it is best just to wait and apply your normal dose the next day. If it is more than 12 hours until the next dose, apply the dose you missed and resume your normal dosing the next day. Do not apply Divigel® more than once each day. If you accidentally spill some of the contents of a Divigel® packet, do not open a new packet. Wait and apply your normal dose the next day.

What should I do if someone else is exposed to Divigel®?

Once you have applied Divigel®, it has dried, and you have washed your hands, there is little risk of transfer to another person. If someone else is exposed to Divigel® by direct contact with the wet gel, that person should wash the area of contact with soap and water as soon as possible. This is especially important for men and children. The longer the gel is in contact with the skin before washing, the chance is greater that the other person will absorb some of the estrogen hormone.

What should I do if I get Divigel® in my eyes?

If you get Divigel® in your eyes, flush your eyes right away with lukewarm tap water. If you have concerns, contact your healthcare provider.

What are the possible side effects of estrogens?

Less common but serious side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

Some of the warning signs of serious side effects include:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

Common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and Vomiting
- Hair loss

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus ("fibroids")
- Vaginal yeast infection

These are not all the possible side effects of Divigel®. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of a serious side effect with Divigel®?

Talk with your healthcare provider regularly about whether you should continue taking Divigel®. If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you. In general, the addition of a progestin is recommended for women with a uterus to reduce the chance of getting cancer of the uterus. See your healthcare provider right away if you get vaginal bleeding while taking Divigel®. Have a breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you otherwise. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often. If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances of getting heart disease. Ask your healthcare provider for ways to lower your chances of getting heart disease.

Have an annual gynecological exam.

General information about safe and effective use of Divigel®

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Divigel® for conditions for which it was not prescribed. Do not give Divigel® to other people, even if they have the same symptoms you have. It may harm them.

Keep Divigel® out of the reach of children.

This leaflet provides a summary of the most important information about Divigel®. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Divigel® that is written for health professionals. You can get more information by calling the toll free number 1-800-654-2299.

How should Divigel® be applied?

- Divigel® should be applied once a day, around the same time each day.
- Apply Divigel® to clean, dry, and unbroken (without cuts or scrapes) skin. If you take a bath or shower, be sure to apply your Divigel® after your skin is dry. The application site should be completely dry before dressing or swimming.
- Apply Divigel® to either your left or right upper thigh. Change between your left and right upper thigh each day to help prevent skin irritation.

TO APPLY:

1. Wash and dry your hands thoroughly.

2. Sit in a comfortable position.
3. Cut or tear the Divigel® packet as shown in Diagram 1.

Diagram 1.

4. Using your thumb and index finger, squeeze the entire contents of the packet onto the skin of the upper thigh as shown in Diagram 2.

Diagram 2.

5. Gently spread the gel in a thin layer on your upper thigh over an area of about 5 by 7 inches, or two palm prints as shown in Diagram 3. It is not necessary to massage or rub in Divigel®.

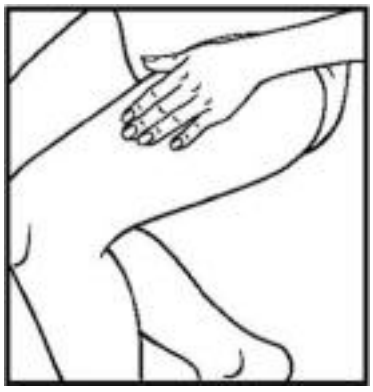


Diagram 3.

6. Allow the gel to dry completely before dressing.
7. Dispose of the empty Divigel® packet in the trash.
8. Wash your hands with soap and water immediately after applying Divigel® to remove any remaining gel and reduce the chance of transferring Divigel® to other people.

HOW IS Divigel® SUPPLIED?

Divigel® is supplied in individual foil packets, each one containing a single day's dose.

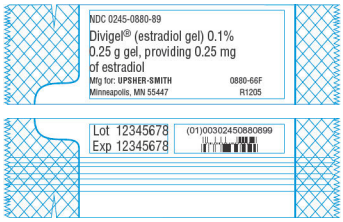
Store Divigel® packets at 20 to 25°C (68 to 77°F). Excursions permitted to 15 to 30°C (59 to 86°F). [See USP Controlled Room Temperature.]

Manufactured by
Orion Corporation Orion Pharma
Tengströminkatu 8
FI-20360 Turku
Finland
Distributed by
Upsher-Smith Laboratories, Inc.
Minneapolis, MN 55447
1-800-654-2299
Product of Finland

PRINCIPAL DISPLAY PANEL - 0.25MG PACKET - FRONT AND BACK

NDC 0245-0880-89

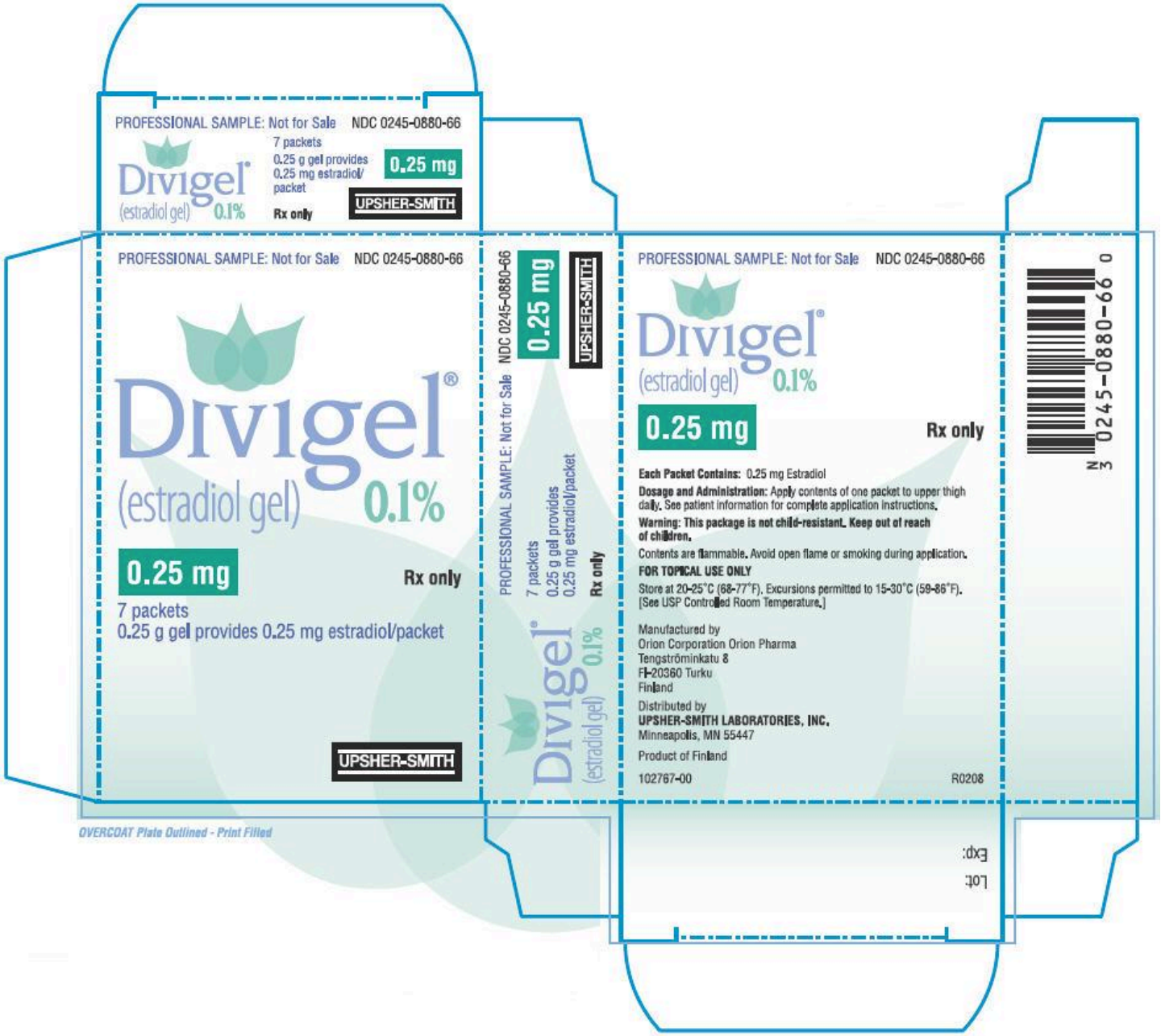
Divigel® (estradiol gel) 0.1%
0.25 g gel, providing 0.25 mg
of estradiol
Mfg for: **UPSHER-SMITH**
Minneapolis, MN 55447
0880-66F
R1205



PRINCIPAL DISPLAY PANEL - 0.25MG/7-PACKET CARTON

PROFESSIONAL SAMPLE: Not for Sale
NDC 0245-0880-66

Divigel®
(estradiol gel) **0.1%**
0.25 mg
Rx only
7 packets
0.25 g gel provides 0.25 mg estradiol/packet
UPSHER-SMITH



PRINCIPAL DISPLAY PANEL - 0.25MG/30-PACKET CARTON

NDC 0245-0880-30

Divigel®

(estradiol gel) **0.1%**

0.25 mg

30 packets

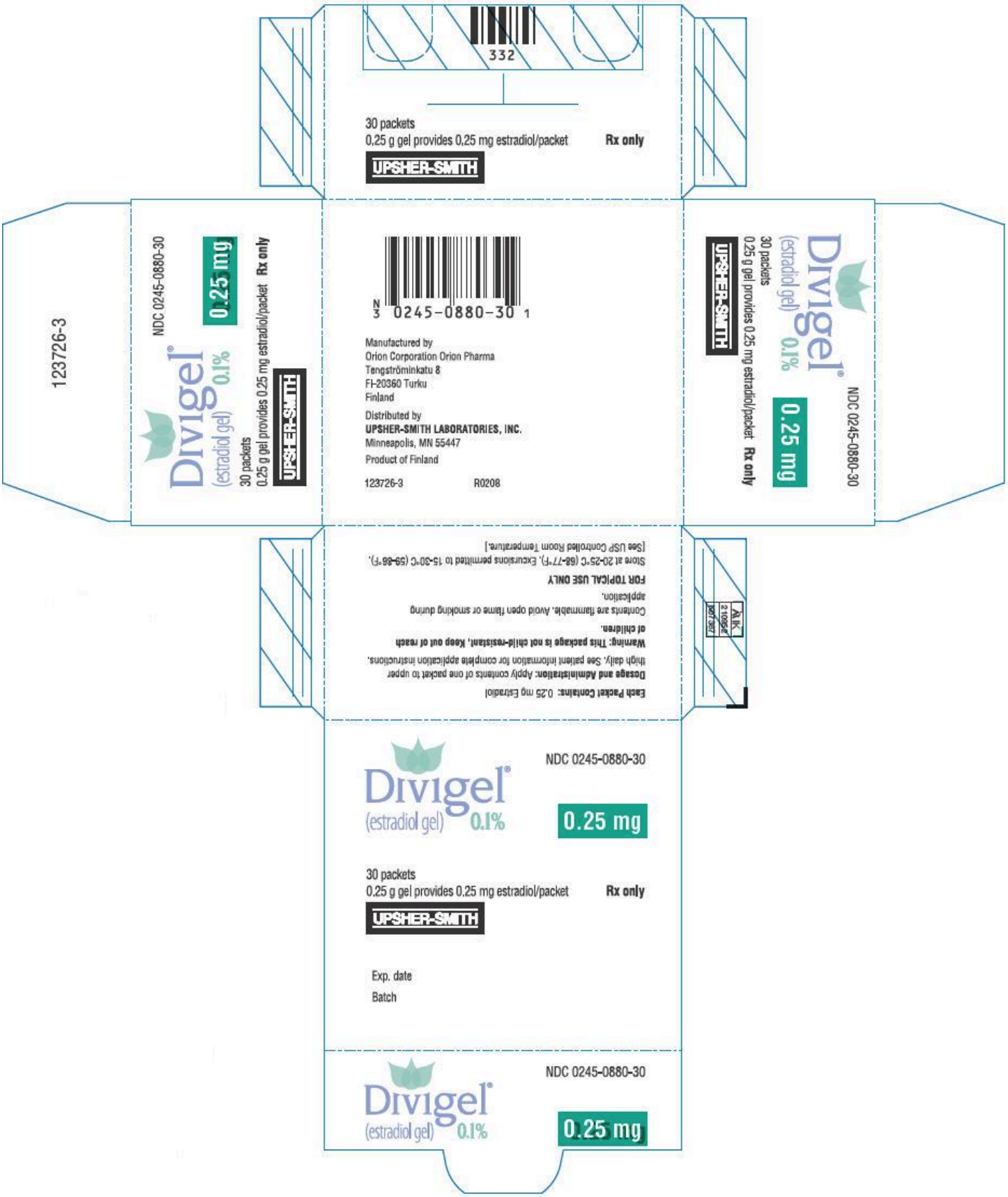
0.25 g gel provides 0.25 mg estradiol/packet

Rx only

UPSHER-SMITH

Exp. date

Batch



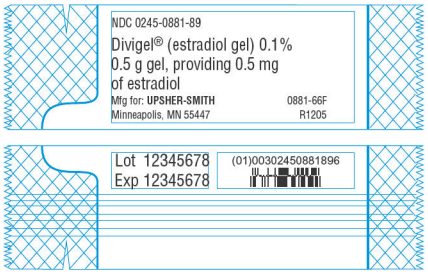
PRINCIPAL DISPLAY PANEL - 0.5MG PACKET - FRONT AND BACK

NDC 0245-0881-89

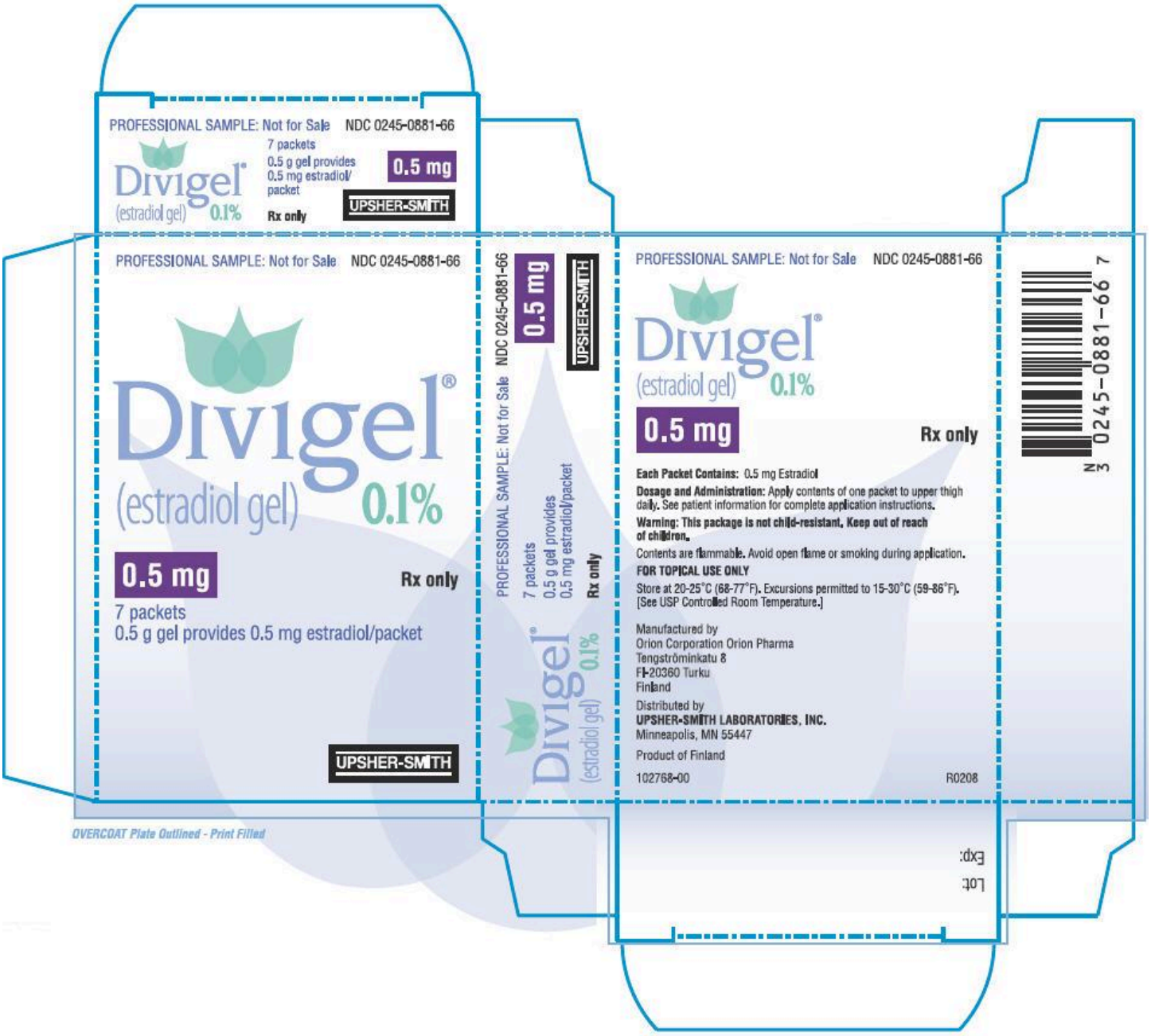
Divigel® (estradiol gel) 0.1%

0.5 g gel, providing 0.5 mg

of estradiol
Mfg for: **UPSHER-SMITH**
Minneapolis, MN 55447
0881-66F
R1205



PRINCIPAL DISPLAY PANEL - 0.5MG/7-PACKET CARTON
PROFESSIONAL SAMPLE: Not for Sale
NDC 0245-0881-66
Divigel®
(estradiol gel) **0.1%**
0.5 mg
Rx only
7 packets
0.5 g gel provides 0.5 mg estradiol/packet
UPSHER-SMITH



PRINCIPAL DISPLAY PANEL - 0.5MG/30-PACKET CARTON

NDC 0245-0881-30

Divigel®

(estradiol gel) **0.1%**

0.5 mg

30 packets

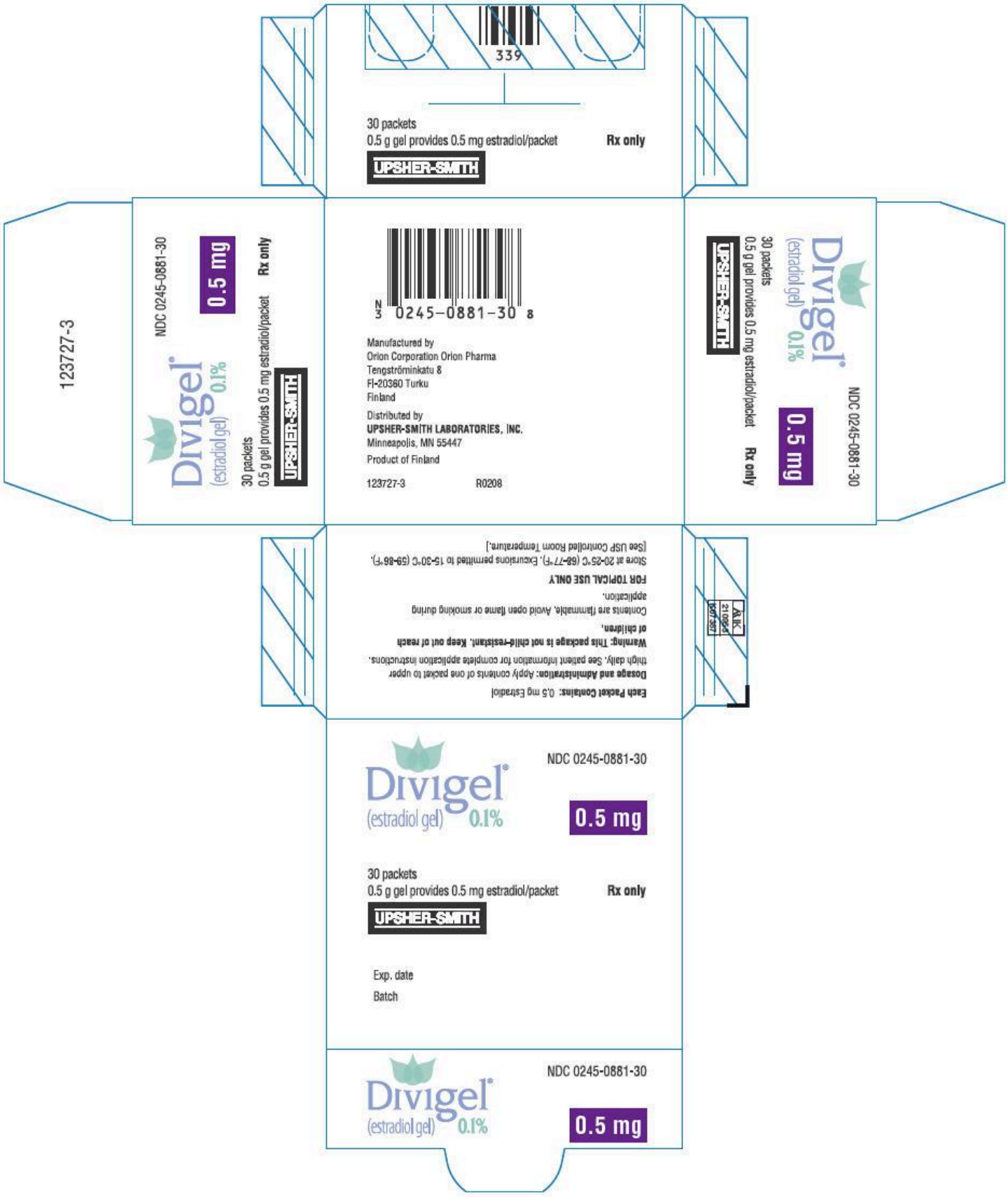
0.5 g gel provides 0.5 mg estradiol/packet

Rx only

UPSHER-SMITH

Exp. date

Batch

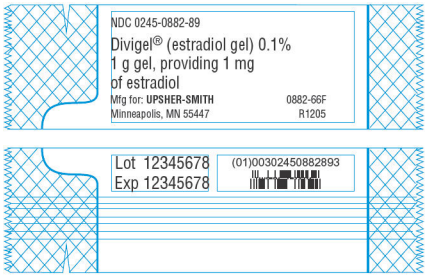


PRINCIPAL DISPLAY PANEL - 1MG PACKET - FRONT AND BACK

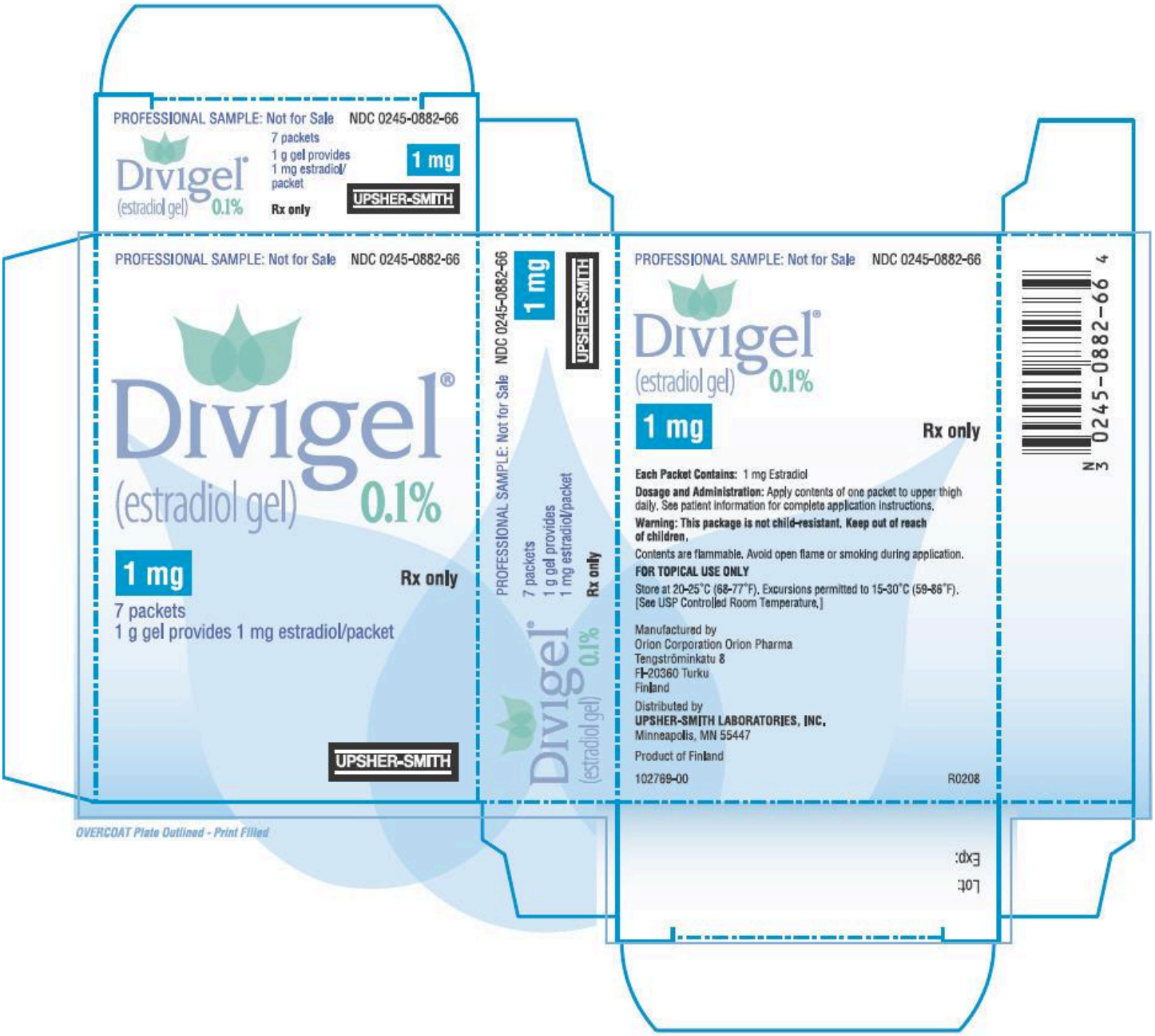
NDC 0245-0882-89

Divigel® (estradiol gel) 0.1%
1 g gel, providing 1 mg
of estradiol

Mfg for: **UPSHER-SMITH**
Minneapolis, MN 55447
0882-66F
R1205



PRINCIPAL DISPLAY PANEL - 1MG/7-PACKET CARTON
PROFESSIONAL SAMPLE: Not for Sale
NDC 0245-0882-66
Divigel®
(estradiol gel) **0.1%**
1 mg
Rx only
7 packets
1 g gel provides 1 mg estradiol/packet
UPSHER-SMITH



PRINCIPAL DISPLAY PANEL - 1MG/30-PACKET CARTON

NDC 0245-0882-30

Divigel®

(estradiol gel) **0.1%**

1 mg

30 packets

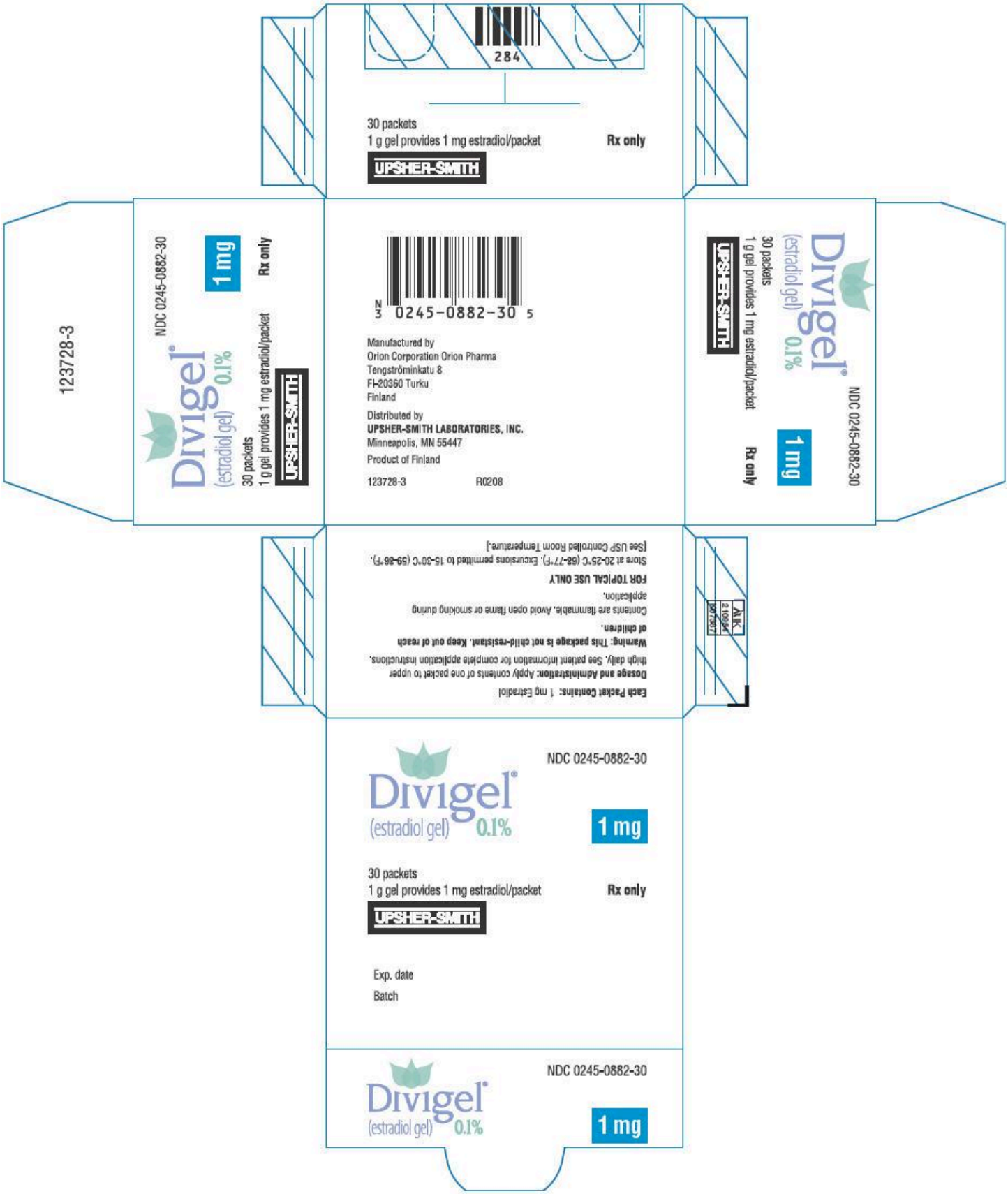
1 g gel provides 1 mg estradiol/packet

Rx only

UPSHER-SMITH

Exp. date

Batch



Revised: 08/2009

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